REMARKS

Claims 1-15 are currently pending in this application.

Applicants have amended claim 9 to recite **2'** instead of **2**. Support for this amendment is seen in original claim 1 and throughout the specification. No new matter is being introduced by this amendment.

A. Rejection under 35 USC 112, second paragraph

The Examiner has maintained rejection of claim 9 under 35 U.S.C. § 112, second paragraph, for being ambiguous, i.e., claim 9 still remains drawn to a composition of formula 1 and formula 2. Applicants have amended claim 9 to remove any ambiguity from the claim, rendering the rejection moot. Withdrawal of the rejection is respectfully requested.

B. Rejections under 35 USC 103(a)

Claims 1-15 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 02/45703 and WO 00/75114. Applicants respectfully traverse because (1) the three criteria needed for a *prima facie* case of obviousness are not met (MPEP § 2142); and (2) greater than expected results are evidence of nonobviousness (MPEP § 716.02).

1. Three Criteria Needed For A *Prima Facie* Case of Obviousness Are Not Met (MPEP § 2142)

A proper obviousness analysis involves a three-step process. First, the Examiner must establish a *prima facie* case of unpatentability based on obviousness. If a *prima facie* case is established, the burden shifts to the applicant to come forward with rebuttal evidence or argument to overcome the *prima facie* case. Finally, the Examiner should evaluate the totality of the facts and all the evidence to determine whether the claimed invention would have been obvious. MPEP § 2144.08 (II).

The standard for obviousness is set out in *Graham v. John Deere Co.* and is based on several underlying factual inquiries, including (1) determining the scope and content of the prior art, (2) resolving the level of skill of a person of ordinary skill in the art, (3) ascertaining the differences between the claimed invention and the teachings of the prior art, and (4) evaluating any objective indicia of non-obviousness, e.g., long-felt need, commercial success, failure of others, copying, unexpected results or other secondary considerations (383 U.S. 17-18, 86 S.Ct. 684).

In considering and determining patentability under 35 U.S.C. § 103, Patent Examiners are responsible for applying the *Graham* factors in each and in every case (MPEP § 2141(I)). Moreover, the Examiner bears the initial burden of factually supporting a *prima facie* conclusion of obviousness, which is established by meeting three basic criteria – (1) suggestion or motivation to modify the reference or to combine reference teachings, (2) reasonable expectation of success and (3) prior art reference (or references when combined) must teach or suggest all the claim limitations (MPEP 2142). As discussed below, the Examiner's combinations of a primary reference with a secondary reference does not meet the requirements necessary to establish a *prima facie* case of obviousness.

Applicants' claim 1 recites a composition comprising one or more salts of tiotropium **1** and one or more pharmacologically acceptable salts of a compound of formula **2'**. Claims 2-15 are directly or indirectly dependent from claim 1.

WO 02/45703 provides a medicament comprising a specific ratio of a compound of formula 1 to a corticosteroid to treat inflammatory or obstructive airway disease. The Examiner asserts that formula 1 of WO 02/45703 is the instantly claimed formula **2'** and that, although the corticosteroid of WO 02/45703 is not the same as tiotropium **1**, it is in the same family as the instantly claimed tiotropium **1**. Applicants respectively disagree with this latter statement because a corticosteroid is a steroid hormone (see Appendix A) and tiotropium **1** is an anticholinergic (see Appendix B) and thus, these compounds are not of the same family. Moreover, WO 02/45703 neither discloses anticholinergics generally nor tiotropium specifically.

WO 00/75114 provides a compound of generic formula 1 for treatment of obstructive or inflammatory disease. According to the Examiner, WO 00/75114 does not specifically teach the instant compound of formula **2'** but that it teaches formula (I) with a small Markush using formula (III) that would make the instant compound obvious. In addition, the Examiner acknowledges that the WO 00/75114 does not specifically teach weight ratios, inhalable powder or propellants but asserts that WO 02/45703 does. Finally, the Examiner purports that WO 00/75114 teaches the combination of formula 1 with other active ingredients such as tiotropium bromide. However, in the latter point, the Examiner fails to acknowledge that the WO 00/75114 specification provides a limited disclosure, i.e., the compounds of formula 1 can be used generally as co-therapeutic agents for use in conjunction with anti-inflammatory or bronchodilatory drug substances, including anticholinergics such as ipratropium bromide, oxitropium bromide and tiotropium bromide (page 17, first

paragraph). Nothing more is taught or suggested, especially with regard to a specific combination of the instantly claimed formula **2'** with tiotropium salts.

The combination of WO 02/45703 with WO 00/75114 does not meet the criteria needed for a *prima facie* conclusion of obviousness because first, there is a lack of motivation or suggestion in the combined reference teachings to arrive at the specific combination taught by the present claims. For example, WO 00/75114 provides numerous possibilities as to what anti-inflammatory or bronchodilatory drug substances "could" be used in conjunction with formula 1. The tiotropium bromide listed therein is one of many compounds disclosed. WO 02/45703 simply teaches formula 1 with a corticosteroid. Second, there cannot be a reasonable expectation of success because a successful combination product will be dependent on a number of experimental variables, including compatibility of components. Finally, the combination of WO 02/45703 with WO 00/75114 does not teach or suggest all the claim limitations as discussed above. For these reasons, applicants respectfully request the rejection for obviousness over WO 02/45703 and WO 00/75114 be withdrawn for failure to meet the criteria necessary to establish a *prima facie* case of obviousness.

2. Unexpected Results Are Evidence Of Nonobviousness (MPEP § 716.02)

In the Reply to Office Action dated November 22, 2005, applicants presented evidence to rebut the Examiner's obviousness rejections via a Declaration of Michael Paul Pieper under 37 C.F.R. § 1.132 (copy attached as Appendix C). This declaration demonstrated unexpected results, i.e., the combination claimed in the present invention is significantly more potent than the use of each active ingredient alone and the synergistic effect is even greater than the calculated sum of the effects of each single component administered alone. In the current Office Action, the Examiner neither acknowledged this evidence nor discussed why this evidence was not persuasive.

The presence of a property not possessed by the prior art is evidence of nonobviousness (In *re Papesch*, 315 F.2d 381 (CCPA 1963). Applicants point out that the WO 00/75114 specification merely comments that the compounds of formula 1 can be used generally as "co-therapeutic agents for use in conjunction with" anti-inflammatory or bronchodilatory drug substances. According to this statement, the compound of formula 1 in WO 00/75114 would have a therapeutic property (if one exists) independent of the anti-inflammatory or bronchodilatory drug substance. In contrast, applicants have demonstrated a

non-obvious result, i.e., a synergistic effect results when using the presently claimed composition. This is neither taught nor suggested by WO 00/75114 or WO 02/45703. Applicants respectively request that Examiner consider this evidence and withdrawal the rejection for obviousness.

C. Conclusion

In view of the above amendments and remarks, applicants respectfully request that Examiner pass this application to issuance. If any points remain at issue which can best be resolved by way of a telephonic or personal interview, the Examiner is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

/wendy petka/

Wendy A. Petka
Attorney for Applicants
Reg. No. 53,459

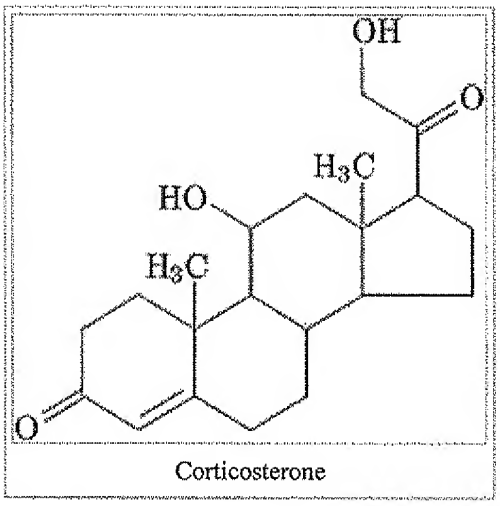
Patent Department
Boehringer Ingelheim Corp.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT. 06877
Tel.: (203) 791-6614
Fax: (203) 798-4408

APPENDIX A

Corticosteroid

From Wikipedia, the free encyclopedia

Corticosteroids are a class of steroid hormones that are produced in the adrenal cortex. Corticosteroids are involved in a wide range of physiologic systems such as stress response, immune response and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior.



Corticosterone

- **Glucocorticoids** such as cortisol control carbohydrate, fat and protein metabolism and are anti-inflammatory by preventing phospholipid release, decreasing eosinophil action and a number of other mechanisms.
- **Mineralocorticoids** such as aldosterone control electrolyte and water levels, mainly by promoting sodium retention in the kidney.

Some common natural hormones are *corticosterone* ($C_{21}H_{30}O_4$), *cortisone* ($C_{21}H_{28}O_5$, 17-hydroxy-11-dehydrocorticosterone) and *aldosterone*.

Uses

Synthetic drugs with corticosteroid-like effect are used in a variety of conditions, ranging from brain tumors to skin diseases. Dexamethasone and its derivatives are almost pure glucocorticoids, while prednisone and its derivatives have some mineralocorticoid action in addition to the glucocorticoid effect. Fludrocortisone (Florinef®) is a synthetic mineralocorticoid. Hydrocortisone (cortisol) is available for replacement therapy, e.g. in adrenal insufficiency and congenital adrenal hyperplasia.

Synthetic glucocorticoids are used in the treatment of joint pain or inflammation (arthritis), dermatitis, allergic reactions, asthma, hepatitis, lupus erythematosus, inflammatory bowel disease (ulcerative colitis and Crohn's disease), sarcoidosis and for glucocorticoid replacement in Addison's disease or other forms of adrenal insufficiency. Topical formulations for treatment of skin, eye diseases (uveitis) or inflammatory bowel disease are available. Corticosteroids are also used supportively to prevent nausea, often in combination with 5-HT3 antagonists (e.g. ondansetron).

Typical undesired effects of glucocorticoids present quite uniformly as drug-induced Cushing's syndrome. Typical mineralocorticoid side effects are hypertension (abnormally high blood pressure), hypokalemia (low potassium levels in the blood), hypernatremia (high sodium levels in the blood) without causing peripheral edema, and metabolic alkalosis.

History

Tadeus Reichstein together with Edward Calvin Kendall and Philip Showalter Hench were awarded the Nobel Prize for Physiology and Medicine in 1950 for their work on hormones of the adrenal cortex which culminated in the isolation of cortisone.

Corticosteroids have been used as a drug treatment for some time. Lewis Sarett of Merck & Co. was the first to synthesize cortisone, using a complicated 36-step process that started with desoxycholic acid, which was

extracted from ox bile. The low efficiency of converting deoxycholic acid into cortisone led to a cost of US $200 per gram. Russell Marker, at Syntex, discovered a much cheaper and more convenient starting material, diosgenin from wild Mexican yams. His conversion of diosgenin into progesterone by a four-step process now known as Marker Degradation was an important step in mass production of all steroidal hormones, including cortisone and the birth control pill. In 1952, D.H. Peterson and H.C. Murray of Upjohn Co. developed a process that used Rhizopus mold to oxidize progesterone into a compound that was readily converted to cortisone. The ability to cheaply synthesize large quantities of cortisone from the diosgenin in yams resulted in a rapid drop in price to US $6 per gram, falling to $0.46 per gram by 1980. The research of Percy Julian also aided progress in the field. The exact nature of cortisone's anti-inflammatory nature remained a mystery for years after however, until the leukocyte adhesion cascade and the role of phospholipase A2 in the production of prostaglandins and leukotrienes was fully understood in the early 1980s.

See also

- Cushing's syndrome
- Vitiligo
- Steroids (general term)
- Fluorometholone

Category: Corticosteroids

APPENDIX B

Anticholinergic

From Wikipedia, the free encyclopedia
(Redirected from Anticholinergics)

An **anticholinergic** agent is a member of a class of pharmaceutical compounds which serve to reduce the effects mediated by acetylcholine in the central nervous system and peripheral nervous system.

Anticholinergics are typically reversible competitive inhibitors of one of the two types of acetylcholine receptors, and are classified according to the receptors that are affected: **antimuscarinic** agents operate on the muscarinic acetylcholine receptors, and **antinicotinic** agents operate on the nicotinic acetylcholine receptors. The majority of anticholinergics are antimuscarinics.

Effects

When a significant amount of anticholinergic is taken into the body, a toxidrome known as **acute anticholinergic syndrome** may result. This may happen accidentally or intentionally as a form of recreational drug use. This class of drug is usually considered the least "fun" by experienced drug users. Because most users do not enjoy the experience, they don't use it again, or very rarely. Risk of addiction is low in the anticholinergic class. Effects are usually more pronounced in the elderly, due to the decrease of acetylcholine production associated with age.

Possible effects of anticholinergics include:

- Ataxia; loss of coordination
- Decreased mucus production in the nose and throat; consequent dry, sore throat
- Xerostomia or dry mouth
- Cessation of perspiration; consequent increased thermal dissipation through the skin leading to hot, red skin
- Increased body temperature
- Pupil dilation (mydriasis); consequent sensitivity to bright light (photophobia)
- Loss of accommodation (loss of focusing ability, blurred vision — cycloplegia)
- Double vision (diplopia)
- Increased heart rate (tachycardia)
- Urinary retention
- Diminished bowel movement, sometimes ileus
- Increased intraocular pressure, dangerous for people with narrow-angle glaucoma

Possible effects in the central nervous system resemble those associated with delirium, and may include:

- Confusion
- Disorientation
- Agitation
- Respiratory depression
- Short-term memory loss
- Inability to concentrate
- Wandering thoughts; inability to sustain a train of thought
- Incoherent speech
- Wakeful myoclonic jerking
- Unusual sensitivity to sudden sounds
- Illogical thinking
- Photophobia
- Visual disturbances

    - Periodic flashes of light
    - Periodic changes in visual field
    - Noisy vision
    - Restricted or "tunnel vision"
- Visual, auditory, or other sensory hallucinations
    - Warping or waving of surfaces and edges
    - Textured surfaces
    - "Dancing" lines; "spiders", insects
    - Lifelike objects indistinguishable from reality
- Rarely: seizures, coma and death

Acute anticholinergic syndrome is completely reversible and subsides once all of the toxin has been excreted. Ordinarily, no specific treatment is indicated. However, in extreme cases, especially those that involves severe distortions of mental state, a reversible cholinergic agent such as physostigmine may be used.

Plant sources

The most common plants containing anticholinergic alkaloids are:

- *Atropa belladonna* (Deadly Nightshade)
- *Mandragora officinarum* (Mandrake)
- *Hyoscamus niger* (Henbane)
- *Datura* species (Datura)

Pharmaceuticals

- **Unclassified**
    - benztropine (Cogentin®)
- **Muscarinic receptor antagonists**
    - **Belladonna alkaloids**
        - Scopolamine (L-Hyoscine)
        - Atropine (D/L-Hyosycamine)
    - **Synthetic and Semisynthetic**
        - Dicyclomine
        - Flavoxate
        - Ipratropium
        - Oxybutynin
        - Pirenzepine
        - Tiotropium
        - Tolterodine
        - Tropicamide
- **Nicotinic receptor antagonists**
    - **Ganglionic blocking agents**
        - Trimethaphan
    - **Nondepolarizing neuromuscular blocking agents**
        - Atracurium
        - Doxacurium
        - Mivacurium
        - Pancuronium
        - Tubocurarine
        - Vecuronium
    - **Depolarizing neuromuscular blocking agents**
        - Suxamethonium chloride

Many other drugs have anticholinergic properties, including cyclic antidepressants and the common allergy medications diphenhydramine (Benadryl) and its 8-chlorotheophylline salt dimenhydrinate (Dramamine), which are used medically for antihistaminergic and antiemetic purposes, and sometimes recreationally for their psychoactive effects. The common side effects of some SSRI antidepressants, such as Prozac (fluoxetine), often sweaty palms, are due to anticholinergic properties.

Some drugs, such as hydrocodone, are mixed with small amounts of an anticholinergic, such as Homatropine Methylbromide to discourage abuse.

Retrieved from "http://en.wikipedia.org/wiki/Anticholinergic"

Categories: Anticholinergics | Psychedelics, dissociatives and deliriants

APPENDIX C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Ingo Konetzki *et al.*	Examiner:	D.Margaret Seaman
Serial No.:	10/717,868	Group Art Unit:	1625
Filed:	November 19, 2003	Docket:	1/1428

For: TIOTROPIUM-CONTAINING PHARMACEUTICAL COMBINATION FOR INHALATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF MICHAEL PAUL PIEPER UNDER 37 C.F.R. § 1.132

Sir:

I, Michael Paul Pieper, declare that:

1. I have studied Veterinary medicine at the University (School of Veterinary Medicine Hannover) Hannover, Germany from 1986 to 1991 (Degree: board certified veterinarian).

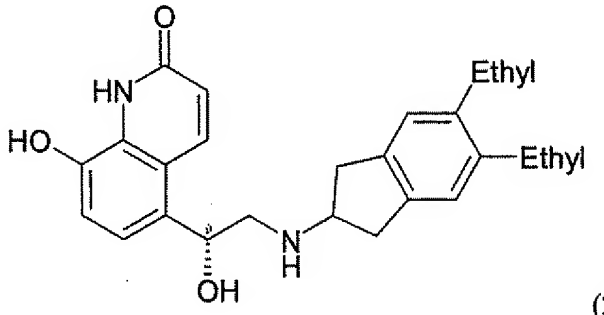
2. I did my doctoral thesis in Pharmacology from 1992 to 1994 and received a VMD (Dr. med. vet.) from the School of Veterinary Medicine Hannover, Hannover, Germany in 1994.

3. Since 1994, I have been employed by Boehringer Ingelheim, presently in the Department of Pulmonary Research of Boehringer Ingelheim Pharma GmbH & Co. KG, Germany.

4. I am a coinventor of the above-identified patent application and I am familiar with the above-identified patent application (hereinafter "the Konetzki *et al.* application").

5. I am familiar with the U.S.P.T.O. Office Action dated June 13, 2003 and the prior art references cited therein: WO 00/75114 and WO 02/45703.

6. Under my responsibility and control, investigations with inhalative administration of the bronchospasmolytic test compounds tiotropium bromide and the compound of formula (2a)



(2a),

in form of its R-enantiomer and as the maleinat acid addition salt (hereinafter "compound (2a)") were conducted according to the experimental protocol described in ANNEX 1.

7. The results of experimental tests according to the protocol of ANNEX 1 are summarized in ANNEX 2. Tiotropium as well as compound (2a) induced a time dependent protection against ACh-induced bronchoconstrictions. Tiotropium and compound (2a) initially reduced the ACh-induced bronchoconstrictions by 40% and 37%, respectively. Over 24 hours, these effects, however, attenuated. A maximally expected additive effect was calculated adding bronchoprotection values of both compounds for each time point (see ANNEX 2, table column C). To summarize the experimental results above, the combination tiotropium bromide with compound (2a) reduced the ACh-induced bronchoconstrictions significantly more potent than the reduction of the ACh-induced bronchoconstrictions achieved using tiotropium or compound (2a). Furthermore, the reduction of the ACh-induced bronchoconstrictions of the combination was greater than the calculated sum of the effects of each single component administered alone.

8. From the above experiments and results, I conclude that the combinations according to the invention of the above-identified patent application, as exemplified by tiotropium bromide and compound (2a), display an unexpected beneficial and synergistic effect which is even greater than the calculated sum of the effects of each single component administered alone.

11. Furthermore, I conclude that these surprising properties of the combinations according to the invention of the above-identified patent application were neither taught, suggested, nor deducible by the cited prior art. Moreover, I conclude that these findings would have been both surprising and unexpected to one of ordinary skill in the art at the time the invention was made.

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: November 3rd, 2005 Signature: 

(Michael Paul Pieper)

ANNEX 1

Method for the Determination of Bronchoprotection Against Acetylcholine-Induced Bronchospastic Collapse in male beagle dogs

Animals were anesthetized with an intravenous bolus of approx. 10 mg/kg propofol (2 % solution) and ventilated using an endo-tracheal tube. Anaesthesia was maintained by a continuous i.v. infusion of propofol (approx. 30 mg/kg/h). The endotracheal tube was connected to a heated pneumotachograph (Fleisch Nr.1, Hugo Sachs Elektronik, March-Hugstetten) in order to measure lung function measurement. Pulmonary resistance was calculated from the simultaneous measurement of transpulmonary pressure and respiratory flow using the isovolumetric method from the respiratory flow calculator of the Notocord software.

Measurements for respiratory resistance, respiratory pressure and dynamic lung compliance were taken prior to the administration of the test compounds (single compounds or drug combinations, respectively) to establish the baseline values. Further measurements were made 10 min, 30 min, 6 hours, 12 hours and 24 hours after administration of the test compound(s). Compounds were administered by inhalation using a new soft mist inhaler (Respimat®, Boehringer Ingelheim Pharma KG) into the endo-tracheal tube.

At each time point bronchoconstriction was induced by i.v. administration of 10 µg/kg acetylcholine (= ACh-challenge). The inhibitory effect was expressed as the percent inhibition calculated using the mean of the two responses to ACh-challenge prior to administration of the compounds. Between the last 3 measurements time points the dogs were allowed to awake.

Dogs were randomized into tree groups each consisting of n=3 animals. Group A received 1.0 µg tiotropium bromide, group B received 48 µg compound (2a) and group D received the combination thereof.

ANNEX 2

Results obtained according to the test protocol of ANNEX 1

In the table below the effects of tiotropium bromide (1 µg/kg) on ACh-induced bronchoconstriction in anaesthetized beagle dogs are outlined in column A, effects of compound (2a) (48 µg/kg) are outlined in column B and the effects of the combination of tiotropium with compound (2a) are outlined in column D. The calculated sum of A+B is shown in column C. Expressed are means of 3 dogs per group.

time [min]	A		B		C	D	
0.167	8.1	7.4	37.5	2.9	45.6	59.0	6.5
0.5	40.6	11.5	37.0	3.5	77.6	74.5	6.2
6	35.2	7.8	24.0	1.9	59.2	71.2	5.0
12	15.1	8.5	9.1	4.6	24.2	44.2	11.9
24	7.8	4.0	2.7	2.0	10.5	32.3	9.2

The graphic illustration of the results is outlined below.